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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/632,149	CUTHBERTSON, R. ANDREW
	Examiner	Art Unit
	Quang Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2001*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

DETAILED ACTION

Applicants' amendment filed on March 07, 2001 in Paper No. 7 has been entered. Claims 13-22 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Responses to Amendments

The rejection of claims 13-22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of the co-pending Application No. 09/018599 which is now issued as U.S. Patent No. 6,204,251 is maintained for the reasons stated in the Office Action mailed on 10/25/00 in Paper No. 4 (page 9). Applicant's statement indicating to defer addressing the rejection until the instant claims are allowed is not deemed to be sufficient for overcoming this rejection.

The rejection of claims 13-22 under 35 USC 112, First Paragraph is partially withdrawn in light of Applicant's arguments and submitted post-filing arts. The following is a scope rejection of claims 13-22 under 35 USC 112, First Paragraph based on the issues already set forth in the Office Action mailed on 10/25/00 in Paper No. 4 (pages 4-7).

Claim Rejections - 35 USC § 112

Claims 13-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a degeneration of ocular

cells as a result of a genetic ocular disease in an animal comprising direct administering to ocular cells a recombinant adenovirus or adeno-associated virus vector comprising a DNA sequence encoding a protein associated with said ocular disease, whereby said DNA sequence is expressed, so as to alleviate the degeneration of said ocular cells; and a method of treating an ocular disease associated with a lysosomal storage defect in an animal comprising direct administering to ocular cells a recombinant adenovirus or adeno-associated virus vector comprising a DNA sequence encoding a lysosomal enzyme, whereby said DNA sequence is expressed, so as to cause a reduction of a lysosomal disease phenotype in said animal, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a genetic ocular disease comprising incorporating exogenous nucleic acid into an *in situ* ocular cell under conditions permissive for the uptake of said exogenous nucleic acid, said exogenous nucleic acid encoding a protein associated with said ocular disease, whereby said exogenous nucleic acid is expressed, and thereby treating said genetic ocular disease. The claims are drawn to the same method wherein said genetic ocular disease is autosomal retinitis pigmentosa, autosomal dominant retinitis punctata albescens, butterfly-shaped pigment dystrophy of the fovea, adult vitelliform macular dystrophy, Norrie's disease, blue cone monochromasy, choroideremia or gyrate atrophy. Claim 22

is directed to the same method wherein an animal having an ocular disease associated with a lysosomal storage disease.

The specification discloses that following superficial epithelial debridement (surgical removal of superficial epithelial cells) and upon topical application of β-galactosidase expressing recombinant adenoviral vector on the corneal surface for 30 minutes, extensive β-galactosidase expression was noted in the corneal epithelial cells of treated rats. Similarly, the specification teaches that upon administering replication-deficient β-galactosidase expressing recombinant adenoviral vector into anterior chamber of the eye, positive staining of the majority of cells lining the posterior surface of the cornea or the corneal endothelial cells was observed for treated rats. Similar injection of the recombinant adenoviral vector into the vitreous humor of the eye of treated rats, positive staining of some of the cells of the choroid was detected for β-galactosidase expression.

The above evidence has been noted and considered along with the submitted post-filing arts in the Amendments filed on March 07, 2001 in Paper No. 7. However, they can not be extrapolated to the instant broadly claimed invention which is drawn to a method of treating a genetic ocular disease and an ocular disease associated with the lysosomal storage disease. The nature of the instant claimed invention falls within the realm of gene therapy. The specification is not enabled for the instant broadly claimed invention because at the effective filing date of the present application (October 31, 1994), gene therapy was an immature and highly unpredictable art and because of the issues discussed below.

It has been noted that there are several factors limiting **an effective gene therapy**, and these include suboptimal vectors, a lack of a long term and stable gene expression, and a lack of an efficient gene delivery to target tissues or cells. The instant claims encompass a method of treating a genetic ocular disease and an ocular disease associated with a lysosomal storage disease. As the term "treating" is well known in the art and treating a disease encompasses producing a useful result, alleviating the effect of a disease, **curing**, **stabilizing** and slowing the decline of a disease (See Amendment filed on March 07, 2001 in Paper No. 7, page 8, lines 2-7). The instant specification fails to provide sufficient guidance demonstrating that any genetic ocular disease or any ocular disease associated with a lysosomal storage disease could be cured or stabilized by the methods of the present invention. Relevant information regarding to specific vector constructs comprising specific transgenes, appropriate dosages of recombinant vectors used, the route of delivery and regimen utilized to **cure** or **stabilize** a particular genetic ocular disease or an ocular disease associated with a lysosomal storage disease are not taught by the instant specification. Since the prior arts at the effective filing date of the present application also did not provide such guidance, coupled with the immature and unpredictable nature of the gene therapy art, it would have required undue experimentation without a predictable expectation of success for one of skilled in the art to make and use the full scope of the instant claimed invention.

The instant claims encompass any and all routes of delivering an exogenous nucleic acid encoding a protein associated with a genetic ocular disease or an ocular disease associated with a lysosomal storage disease into an animal. This is because

the term "*in situ* ocular cell" is merely defined as an ocular cell contained within the eye (see specification, page 6, lines 10-12) and the term "conditions permissive for the uptake of exogenous nucleic acid" is meant experimental conditions which allow the *in situ* ocular cell to take up and be transformed with the exogenous nucleic acid (specification, page 10, line 32 continues to line 4 of page 11). However, the instant specification fails to provide sufficient guidance demonstrating that therapeutic effects could be obtained by all routes of delivering an exogenous nucleic acid encoding a protein associated with an ocular disease into an animal (e.g. a systemic delivery through the vascular system), such that said nucleic acid could be taken up and expressed by the target ocular cells efficiently to yield the desired therapeutic results. As noted above, the lack of an efficient gene delivery to target tissues or cells is one of several factors known to limit the effectiveness of gene therapy. Moreover, even in the most recent review on available gene delivery systems, Wivel & Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there **will be** multiple vectors **specifically designed for certain organ sites and certain diseases**.....It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section of Hematol. Oncol. Clin. North Am. 12:483-501, 1998). Also noted in the previous Office Action, the instant specification fails to address issues such as the fate of delivering and uptake of

exogenous nucleic acid and the fraction of exogenous nucleic acid taken up by target cells (ocular cells in this instance). These factors differ dramatically based on which route of administering the exogenous nucleic acid into an animal being utilized and subsequently the desired therapeutic effects being sought. Therefore, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation without a predictable expectation of success for a skilled artisan to make and use the broadly claimed invention.

The instant claims also encompass the use of any and all vectors for delivering exogenous nucleic acid to an *in situ* ocular cell, such as retrovirus and herpes simplex virus vectors. It is noted that in many of the claimed genetic ocular diseases wherein primarily differentiated photoreceptors express mutated genes, for example mutated opsin, the β subunit of rod cGMP phosphodiesterase, peripherin/*rds* and others in retinitis pigmentosa, the specification fails to provide guidance for one of skill in the art on how an effective delivery of an exogenous nucleic acid in the form of a retrovirus vector could be achieved in such postmitotic cells in order to achieve any therapeutic effect, since retroviral vectors require target cell proliferation for gene transfer. At about the effective filing date of the present application, Li et al. (Investigative Ophthalmology and Visual Science 35:2543-2549, 1994) noted that although replication-deficient herpes simplex virus 1 (HSV-1) may hold promise for gene transfer to postmitotic neurons, but the current versions of HSV-1 based vectors are cytotoxic, and the difficulty in obtaining a high titer HSV-1 for an efficient gene transfer (See column 2, second paragraph, page 2543 and column 2, second paragraph, page 2547). Apart

from the exemplification showing an efficient expression of β-galactosidase in various ocular cells mediated by a replication-deficient recombinant adenovirus, the instant specification fails to provide sufficient guidance demonstrating that a similar gene-transfer in ocular cells could be mediated by any other recombinant viral vectors such as retrovirus or HSV-1 or Epstein-Barr virus or non-viral vectors such as plasmids or liposomes containing exogenous nucleic acid as contemplated by the present invention. In the absence of such guidance provided by the specification, it would have required undue experimentation for a skilled artisan to make and use the full scope of the instant claimed invention.

Accordingly, due to the lack of sufficient guidance provided by the instant specification regarding to the full intended scope of treating a genetic ocular disease or an ocular disease associated with a lysosomal storage disease, the unpredictable nature of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on March 07, 2001 in Paper No. 6 (pages 2-7) have been fully considered.

Applicants argued that the submitted post-filing arts fully support the enablement of present specification for therapeutic use of ocular gene therapy (page 3, lines 3-5 in the Amendment). However, Examiner respectfully disagrees with Applicants that the

post-filing arts **fully support the entire scope of the instant claimed invention** for the reasons discussed below.

Bennett et al. (Exhibit A) showed that through **subretinal injection** of a recombinant replication-defective **adenovirus** comprising the murine cDNA encoding for a wild type cGMP phosphodiesterase (βPDE) in the *rd* mouse **resulted in the delay of photoreceptor cell death by six weeks** (see abstract and Fig. 4). Bennett et al. also stated that "It will be essential to correlate the histological defects with quantitative data regarding visual function" (page 652, col. 2, last paragraph) and "It will be especially important in such studies to determine the percentage of the retina that should be treated to obtain optimal visual function....Although only a small portion of the retina was treated, it **would be possible** to treat large areas of, or even the entire retina with this procedure" (col. 2, last paragraph continues to line 2 of col. 1 on page 653).

Akimoto et al. (Exhibit B) demonstrated that **injection into the subretinal space** of Royal College of Surgeon rats having inherited retinal dystrophy with a **recombinant adenovirus vector** expression bFGF significantly **delayed photoreceptor cell death** as measured by the thickness of the outer nuclear layer (see abstract and Fig. 5).

Li et al. (Exhibit C) also showed that **direct intraocular delivery of a recombinant adenovirus** expressing the human β-glucuronidase into the eyes of mice with mucopolysaccharidosis VII resulted in a significant correction of the lysosomal storage phenotype, reduction of the storage vacuoles, in retinal pigment epithelium (RPE) cells (see abstract). Li et al. further stated that "Although not investigated in this work, **we speculated that photoreceptor structure and function may improve** if

followed for longer periods after correction of the RPE phenotype (page 7704, col. 1, last sentence of first full paragraph).

The summarized results of the studies of Bennett et al., Akimoto et al. and Li et al. outlined above as well as the reported positive results for other references cited by Applicants clearly indicate that **a cure** or **stabilization** of a genetic ocular disease or an ocular disease associated with a lysosomal storage disease have not been achieved or established. The delay of photoreceptor cell death and the reduction of storage vacuoles in RPE cells are not deemed to be equivalent to a cure or the stabilization of an ocular disease as encompassed by the full scope of treatment contemplated by Applicants. Furthermore, there is no established correlation between the reported positive results with the ultimate proper visual functions in the treated animals. Additionally, even in the most recent review on gene therapy for ocular disease, Bennett and Maguire (Mol. Ther. 1:501-504, 2000) stated that "[t]here has not, as yet, been **a demonstration of cure using gene therapy approaches**...." (page 501, col. 1, middle of the first paragraph), and "There is currently **no cure** for retinitis pigmentosa and existing treatments are of **uncertain or limited benefit in retarding the progression** of the disease" (page 502, col. 2, middle of first full paragraph). Also a cure and a stabilization for an ocular disease through gene therapy is highly unlikely because of the lack of a long term and stable therapeutic transgene expression *in vivo* as noted above and in the previous Office Action. This is supported by Bennett et al. (Exhibit A) who stated that "The ability to interfere with retinal degeneration in humans will depend on the stability of the transduced genes. **Ideally**, for application to the slowly progressive

human diseases, the transgene-expressing cells should persist over years or even decades. Although we have observed transgene expression in transduced retinal cells at least 100 days after injection, **the number of expressing cells diminishes with time**" (page 652, col. 2, top of the first full paragraph). The transient transgene expression *in vivo* is well known in the gene therapy art in general, and it is attributed as one of the factors limiting the effectiveness for gene therapy (Dang et al., Clin. Cancer Res. 5:471-474, 1999, page 474, col. 2, last paragraph). Therefore, at the effective filing date of the present application given the lack of guidance provided by the instant specification, it would have required undue experimentation without a predictable expectation of success for a skilled artisan to make and use the full scope of the methods as claimed.

It is also clearly evident from the references cited by Applicants that the reported positive results were obtained only by **direct administration** of recombinant viral vectors (mostly adenovirus) into the eyes of treated animals. As the scope of the instant claims encompasses all delivery routes to achieve contemplated therapeutic results, neither these post-filing references nor the instant specification provide such guidance in this regard. Moreover, Bennett & Maguire stated that "**Systemic delivery of gene therapy agents does not result in gene delivery to ocular structures**" (page 501, col. 1, first sentence of second paragraph). Additionally, vector targeting *in vivo* to desired cells or organs, for this instance ocular cells, is known to be unpredictable and inefficient. This is supported by numerous teachings in the art. As an example, Verma & Somia (Nature 389:239-242, 1997) cited the Office Action in

Paper No. 4 for the parent case 09/018,599, reviewed various vectors known in the art for use in gene therapy and the problems associated with each. They indicated clearly that resolution to *in vivo* vector targeting even several years after the effective filing date of the present application had not been achieved in the art (see the entire article). The instant specification fails to teach a skilled artisan how to overcome the unpredictability for *in vivo* vector targeting such that an efficient transfer and expression of therapeutic transgene to target ocular cells could be achieved by all modes of delivery to achieve the contemplated therapeutic effects. As such, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and use the instant broadly claimed invention.

Applicants further argued that effective treatment of ocular disease using the present invention has also been shown using vectors other than adenovirus as demonstrated by submitted post-filing references (page 4, second full paragraph), and therefore the specification is enabled for the full scope of the claimed invention. Examiner respectfully disagrees with Applicants. The instant claims encompass the use of **any and all vectors** for delivering exogenous nucleic acid to ocular cells to achieve contemplated therapeutic results. It is noted that apart from the references of Jomary et al. (Exhibit D) and Takahashi et al. (Exhibit E) which teach the use of recombinant adenoassociated virus and recombinant HIV to rescue photoreceptor cell degeneration in *rd* mice, respectively, all other cited references demonstrate the use of a recombinant adenoviral vector to achieve the reported positive results. With regard to the reference of Takahashi et al., there is no correlation between this reference and the instant

specification because the present specification does not teach or contemplate the use of a recombinant HIV vector to treat an ocular disease. Applicants are invited to point out the exact page numbers, the line numbers in the instant specification that teach the use of a recombinant HIV vector to treat an ocular disease. As such, until further evidence is provided, on the basis of the present application one of skilled in the art would only be able to achieve positive results in treating animals with an ocular disease via the use of recombinant adenovirus and AAV. However, this is deemed to be insufficient guidance to commensurate with the full scope of the instant claimed invention which encompasses the use of all viral and non-viral vectors for attaining therapeutic results in the methods as claimed. The submitted post-filing arts did not support such a broadly claimed invention. Applicants also failed to provide any factual evidence indicating that recombinant retrovirus or HSV-1 or exogenous nucleic acids in the form of plasmids or liposomes could mediate an efficient transgene delivery and expression in target ocular cells to achieve the desired therapeutic effects. Additionally, even in the year 2000 Bennett & Maguire have noted that recombinant adenovirus, adeno-associated and HIV viruses **are the only vectors that have proven to be useful for gene delivery to ocular cells** (page 501, col. 2, middle of first paragraph and Table 1). Therefore, with the lack of guidance provided by the specification, it would have required undue experimentation without a predictable expectation of success for a skilled artisan to make and use the broadly claimed invention.

Finally, in response to the *In re Wands* factors cited in the previous Office Action, Applicants cited method steps (a) to (d) involved in treating an ocular disease (page 6 of

the Amendment) to demonstrate that the treatment of an ocular disease by the claimed methods is not undue experimentation. Examiner respectfully finds Applicant's argument to be unpersuasive because the mere recitation of method steps (a) to (d) is not deemed to be sufficient guidance for one skilled in the art to overcome the obstacles and the unpredictability of achieving therapeutic effects in treating an ocular disease in an animal via gene therapy by the methods as claimed for the reasons already discussed in the preceding paragraphs.

Accordingly, the rejection of claims 13-22 is maintained under 35 U.S.C. 112, first paragraph for the reasons stated above.

Conclusions

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136 (a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER